REMARKS

I. Issue concerning response to Restriction Requirement of March 31, 2009

In the Office Action issued March 31, 2009, the Examiner presented a two-way restriction of Applicants' claims, as between the following groups:

Group I: Claims 39-73, drawn to a method for treating an individual with a tumor resistant or refractory to a taxane, comprising administering to the individual an effective amount of a compound of the structure provided in claim 39; and

Group II: Claims 74-107, drawn to an article of manufacture and packaged pharmaceutical composition including a label which indicates that said pharmaceutical composition can be used for the treatment of an individual suffering from a cancer or tumor resistant or refractory to a taxane, wherein said pharmaceutical composition comprises a compound of claim 74.

Election of Group

In addition to electing Group I or II for further examination, the Examiner also required election of a particular taxane (if present), election of a specific cancer type, and election of a single anti-cancer therapeutic co-agent (if present).

In the response filed May 29, 2009, Applicants provisionally elected for examination (with traverse) the claims of Group I (i.e., Claims 39-73) drawn to a method for treating an individual with a tumor resistant or refractory to a taxane, comprising administering to the individual an effective amount of a compound of the structure provided in claim 39, for further examination on the merits.

For the required election of species, Applicants elected the method in the absence of a taxane. For a particular cancer/tumor, Applicants elected prostate cancer. And finally, for a particular anti-cancer therapeutic co-agent, Applicants elected the method in the absence of a co-agent.

Applicants stated in the response that the claims readable on the elected species were Claims 39-47, 52-55, 57-65, and 70-72.

Therefore, the subject matter that should presently be under consideration is a method for the treatment of prostate cancer comprising administration of satraplatin and wherein the cancer is resistant or refractory to a taxane and the method does not include administration of a co-agent. The claims readable on this method are as set forth above. However, in the present Office Action on page 2, the Examiner has included among the claims withdrawn from consideration (as a result

of the Restriction being made final) Claims 43, 44, 53, 54, 55, 61, 62, 70, 71, and 72, which are claims included in Applicants' list of claims readable on the elected invention and that were all part of the Examiner's Group I restriction group. As such, Applicants believe the Examiner has mistakenly withdrawn from consideration claims that cover elected subject matter. In addition, on page 3 of the Office Action, the Examiner states that, "Claims 39-44, 45-47, 52, 57-62, and 63-65 are currently under examination and the subject of this Office Action." As can be seen from the Examiner's statement, Claims 43, 44, 61, and 62, which were included in the "withdrawn" group on page 2 are now indicated to be under examination on page 3, however, Claims 53, 54, 55, 70, 71, and 72 are still mistakenly missing from the group of claims that should be under examination.

Applicants assert that Claims 53, 54, 55, 70, and 71 recite subject matter that is readable on the elected invention and it is requested that these claims be rejoined and included with the claims currently under examination.

II. 35 U.S.C. §112, first paragraph

The Examiner has raised an objection under 35 U.S.C. §112, first paragraph against Claims 39-44, 45-47, and 59-60. According to the Examiner,

> "[T]he specification, while being enabling for treatment of a resistance or refractoriness to prostate cancer to taxane wherein the resistance or refractorness [sic] is not mediated by tubulin or an ABC transporter, **does not reasonably provide enablement for resistance or refractoriness to prostate cancer mediated through tubulin or overexpression of an ABC transporter**." (See, Office Action, page 3; emphasis in original.)

According to the Examiner,

> "[T]he instant specification . . . lacks adequate guidance, direction or discussion to apprise the skilled artisan how the claimed compound may be used to achieve the disclosed utilities for treatment of prostate cancer via mediation of tubulin or overexpression of an ABC transporter . . ." (See, Office Action, page 4.)
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> "In the instant case, the information that is missing is a clear correlation between the claimed compound and its efficacy in treating the disclosed conditions, either through specific evidence in the form of data demonstrating such a fact or at least a sound mechanistic correlation between the claimed compound, *its ability to function in such a manner* and the amenability of the

> claimed disease state to treatment using an agent capable of functioning in this manner." (See, Office Action, page 5; emphasis in original.)

Applicants respectfully assert that the specification provides ample data, guidance, direction and discussion to convince one skilled in the art that satraplatin is an effective treatment for prostate cancer that is resistant or refractory to a taxane, regardless of whether the resistance or refractoriness is mediated through tubulin or overexpression of an ABC transporter. In addition, the data in the specification do, in fact, provide a clear correlation between the functionality of satraplatin via art-accepted models of cancer treatment and its capability for treating a cancer that is resistant or refractory to a taxane where the resistance is mediated through tubulin or overexpression of an ABC transporter according to the manner described.

First, the specification provides direct teachings, beginning on page 17, regarding the resistance to taxanes in cancer treatment as well as the possible modes of action of taxanes and mechanisms of acquired resistance to cancer treatment,

> "Taxanes exert their cytotoxic effect by binding to tubulin, thereby causing the formation of unusually stable microtubules. The ensuing mitotic arrest triggers the mitotic spindle checkpoint and results in apoptosis." (See, specification, page 17, lines 21-23.)
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> "Known mechanisms that confer taxane resistance include, for example, molecular changes in the target molecules molecules [sic], i.e., α-tubulin and/or β-tubulin, upregulation of P-glycoprotein (multidrug resistance gene MDR-1) . . ." (See, specification, page 19, lines 10-12).

As set forth in the specification, one mechanism for overexpression of an ABC transporter is mediated through P-glycoprotein,

> "Experimental models demonstrate that multidrug resistance can be caused by increased expression of ATP-binding cassesette [sic] (ABC) transporters, which function as ATP-dependent efflux pumps. These pumps actively transport a wide array of anti-cancer and cytotoxic drugs out of the cell, in particular natural hydrophobic drugs. In mammals, the superfamily of ABC transporters includes P-glycoprotein [P-gp] . . ." (See, specification, page 26, lines23-27.)
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> "In a preferred embodiment, the drug resistance of the tumor is mediated through overexpression of an ABC transporter. In a further preferred embodiment, the drug resistance of the tumor is

> mediated through the overexpression of P-gp. Numerous mechanisms can lead to overexpression of P-gp, including amplification of the MDR-1 gene . . ." (See, specification, page 27, lines 12-16.)

Therefore, the specification first discloses that resistance of cancer cells to taxanes is mediated through a number of mechanisms including tubulin (e.g., formation of unusually stable microtubules) and overexpression of ABC transporters (e.g., overexpression of P-glycoprotein (P-gp)).

Secondly, the specification provides scientific data presented with art-accepted models of cancer treatment, which models specifically demonstrate resistance of cancer cells to treatment with taxanes where the resistance is mediated through tubulin or overexpression of ABC transporters and that this resistance can be effectively overcome by treatment with compounds according to the present invention.

For example, as set forth in the specification, in tumor cells where the taxane resistance is mediated through tubulin, Applicants demonstrated that cancer cells that are highly resistant to the taxanes paclitaxel and taxotere were yet highly susceptible to treatment with satraplatin (JM216) as well as the satraplatin metabolites JM118 and JM383. As described in Example IB, beginning on page 51, tubulin mutated, paclitaxel-resistant human ovarian carcinoma cells derived from cell line 1A9-PTX10 were treated with either paclitaxel, taxotere, satraplatin (JM216), JM118, or JM383 and the results are presented in Table 1. As seen in Table 1, (page 53) the relative resistance of these tumor cells to paclitaxel and taxotere was high, 42.6 and 105.8, respectively. In sharp contrast, these cancer cells were highly susceptible to satraplatin and satraplatin derivatives: relative resistance to JM216, JM118 and JM383, was 1.3, 3.1, and 2.1, respectively.

Similarly, as also presented in Table 1, NCI-Adr-resistant tumor cells having a taxane resistance that is mediated through P-glycoprotein (overexpression of an ABC transporter), were highly resistant to paclitaxel and taxotere (relative resistance of 46 and 33, respectively) but highly susceptible to treatment with JM216, JM118, and JM383 (relative resistance 1.1, 1.1, and 0.93 respectively).

Therefore, the specification and data clearly demonstrate this embodiment of the invention, i.e., a method for treating a cancer resistant or refractory to a taxane where the resistance is mediated through tubulin or overexpression of an ABC transporter comprising administering an effective amount of satraplatin or satraplatin metabolite.

In another tumor cell cancer model where the resistance is mediated through an ABC transporter, colon carcinoma cells (HT29/MIT), were treated with either satraplatin or JM118. As seen in Table 3 on page 56 of the specification, the HT/29/MIT carcinoma cells had a relative resistance to mitoxantrone of 175, however these cells were highly susceptible to satraplatin and JM118 (relative resistance of 1.6 and 1.3, respectively).

Similarly, the etoposide-resistant breast cancer cell line MCF-7/VP, a cell line whose resistance is also mediated through an ABC transporter, had a relative resistance to etoposide of >20, however these cells were highly susceptible to satraplatin and JM118 (relative resistance of 1.6 and 1.1, respectively).

Therefore, the specification clearly demonstrates, by presenting data in art-accepted models for cancer treatment, that cancer cells having a resistance to taxane treatment are highly susceptible to treatment with satraplatin and derivatives thereof. Moreover, much of the data presented relate to treatment of cell types wherein the mechanism of refractoriness toward taxanes is believed to be known, namely, taxane resistance is mediated by mutation of tubulin or mediated through overexpression of an ABC transporter. Therefore, the Examiner's argument that the specification is not enabling for treatment of refractory cancers, particularly cancers wherein taxane resistance is mediated through tubulin or overexpression of an ABC transporter, is incorrect and contrary to the data directly in front of the Examiner.

No evidence has been presented to show that cancers having taxane resistance mediated by any mechanism *other than* those explored in Applicants' working examples would not also be susceptible to treatment according to Applicants' teachings. Accordingly, Applicants are not faced with any reason for being bound to a particular mechanism of action for their therapeutic, satraplatin, and have taught the field that satraplatin is effective against taxane-resistant tumors, regardless of the mechanism of the taxane resistance. Confirmation of effectiveness for any other resistant tumor may be tested by following in a slavish manner the Applicants' working examples, and such is not undue experimentation. Accordingly, it is respectfully submitted that the claims as written are completely enabled by the original specification as filed.

In view of the foregoing remarks and the data originally presented in the application, reconsideration and allowance of Claims 39-44, 45-47, and 59-60 are respectfully requested.

III. 35 U.S.C. §103

The Examiner has raised an objection to Claims 39-44, 45-47, 52, 57-62, and 63-65 under 35 U.S.C. §103 as being unpatentable over W. Jia, U.S. Pat. No. 6,759,397 ("Jia"), and P. Bednarski, *Current Opinion In Oncologic, Endocrine & Metabolic Investigational Drugs*, 1(4):

448-458 (1999) ("Bednarski"), in view of Rowinsky et al., *The New England Journal of Medicine*, 332(15): 1004-1014 (1995) ("Rowinsky et al."), and J. Masferrer, U.S. Pub. No. 2004/0072889 ("Masferrer").

With respect to Jia, the Examiner states,

> "Jia et al. [sic] teaches that cisplatin and Rh2 is administered to non-Pgp containing multidrug resistant prostate cancer and are synergistic." (See, Office Action, page 8.)

The Examiner concludes,

> "It would have been obvious to administer to multidrug resistant prostate cancer patients the combination of cisplatin/Rh2 and JM216 because Jia et al. teach that cisplatin/Rh2 is synergistic in non Pgp multiple drug resistant cells and JM216 has potential for the treatment of prostate cancer. Further, one skilled in the art would have been motivated to substitute the functionally equivalent satraplatin for cisplatin since each is a related platin compound." (See, Office Action, page 8.)

As a preliminary matter, Applicants respectfully point out that the Examiner's objection appears to be directed toward subject matter that is not under examination. As stated above, following the prior species election within Group I, the subject matter that should presently be under consideration is a method for the treatment of prostate cancer comprising administration of satraplatin or JM118, wherein the cancer is resistant or refractory to a taxane and the method does not include a co-agent. However, the inclusion of a co-agent (Rh2) appears to be the primary teaching and requirement of the Jia reference that is relied on by the Examiner.

Jia teaches (and claims) that paclitaxel (a taxane) is effective at inhibiting the multiplication of prostate and breast cancer cells when administered to the cells in combination with Rh2, a ginsenoside. (See, Jia, Claim 1.) The only teaching in Jia with respect to cisplatin is set forth in Example 3, beginning in column 7, line 30. Example 3 demonstrates the synergistic effect of cisplatin and Rh2 on mesothelioma cells, a rare cancer that affects the lining of some internal organs and is usually the result of prolonged exposure to asbestos.

Jia has no disclosure related to the treatment of prostate cancer with cisplatin and, even if there was such a disclosure one skilled in the art would never, as alleged by the Examiner, "have been motivated to substitute the functionally equivalent satraplatin for cisplatin since each is a related platin compound". Applicants strongly challenge the Examiner's proposal that cisplatin and satraplatin are functionally equivalent and any suggestion that the person of ordinary skill in the art would regard the two compounds as equivalent or interchangeable. Cisplatin and satraplatin are completely different compounds having completely different structures and modes

of action, and one or ordinary skill in the art would have no basis to assume these compounds have similar effects or that the effects of administering one compound would be indicative or predictive of the effects of administering the other. For example, it is known that satraplatin and cisplatin both bind to DNA in cancerous cells, however satraplatin functions by interfering with cell division whereas cisplatin interferes with cellular repair mechanisms (See, Jia, column 2, lines 50-53.)

In fact, the first page of Applicants' specification discusses problems encountered with cisplatin when administered to human subjects and the significant benefits of using satraplatin over cisplatin including satraplatin's reduced toxicity as compared to cisplatin:

> "Platinum compounds are among the most active chemotherapeutic agent available for the treatment of a variety of malignancies . . . The use of some of these compounds, e.g., cisplatin, is restricted by both toxological and resistance considerations. To overcome these issues, efforts were started to discover novel platinum compounds which do not share these properties of cisplatin. One compound that was identified is satraplatin (JM216), a platinum (Pt) IV complex."[1] (See, specification, page 1, lines 19-24.)
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> **Satraplatin has advantages compared to cisplatin** due to its oral availability and favourable safety profile, such as the absence of kidney- and neurotoxicity." (See, specification, page 1, lines 24-25; emphasis added.)
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> "**Satraplatin is considerably different from cisplatin** due to its oral availability and favourable safety profile, such as the absence of kidney- and neurotoxicity. In addition, there is no cross resistance between satraplatin and cisplatin (citation omitted). Indeed, herein we demonstrate that the efficacy of satraplatin and its metabolite is maintained in cisplatin-resistant tumor cells (Example 4)." (See, specification, page 11, lines 14-18; emphasis added.)

As seen in Example 4, ovarian carcinoma cells (A2780) which were highly resistant to cisplatin (relative resistance = 86), were highly susceptible to treatment with satraplatin (JM216), JM118, and JM383 (relative resistance = 6.8, 2.6, and 1.4, respectively). This is a clear indication that, not only are these two compounds structurally distinct, but clearly their modes of action are different and clearly, as shown in Example 4, the results observed following

[1] Cisplatin is a platinum II complex.

administration of cisplatin are in no way indicative or predictive of the administration of satraplatin, even when administered in the same cancer cell model.

Therefore, in sharp contrast to the Examiner's assertion, satraplatin and cisplatin are in no way functionally equivalent and, based on their known differences, one skilled in the art would never substitute one for the other much less assume they would behave in similar fashion in the treatment of cancer.

None of the remaining cited references, Bednarsky, (JM216 in clinical trials), Rowinsky et al., (paclitaxel is a well known taxane), and/or Masferrer, (cisplatin and satraplatin are both platin antineoplastic agents) teach or disclose the treatment of prostate cancer resistant or refractory to a taxane by administration of satraplatin.

For the reasons set forth above, reconsideration and allowance of all claims readable on the elected invention, i.e., Claims 39-47, 52-55, 57-65, and 70-72 are respectfully requested.

Respectfully submitted,

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